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THE COUNCIL FOR TOBACCO RESEARCH - U.S.A.

110 EAST 59TH STREET
NEW YORK, N. Y. 10022

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Application For Research Grant

Date: 1 January 1974

1. Name of Investigator(s): (include Title and Degrees)

Hans Meier, D.V.M., Dr. med. vet., M.R.S.H., Senior Staff Scientist
R. R. Fox, Ph.D., Staff Scientist, and B. A. Diwan, Ph.D., Research Associate

2. Institution & Address: The Jackson Laboratory, Bar Harbor, Maine 04609

3. Short Title of Project: Transplacental effects of nitrosocompounds in inbred strains of mice and rabbits.

4. Proposed Starting Date: 1 July 1974

5. Anticipated Duration of this Specific Study: 3 years

6. Brief Descripton of Objectives or Specific Aims: Attached

7. Give a Brief Statement of your Working Hypothesis: Attached

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Details of Experimental Design and Procedures: (Attach Separate Pages)

Attached

Physical Facilities Available (Where Other than Administering Organization Indicate Geographical Location)

The Jackson Laboratory, Main Complex, and Hamilton Laboratory, West

Additional Requirements: None

Biographical sketches of all principal and professional personnel (append)

Attached

List of publications: (Five most recent as pertinent) (append)

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13. Budget: (1st year)

	% time	Amount
A. Salaries (Personnel by names)		
Professional		
Hans Meier, Project Director	5	$ REDACTED
R. R. Fox, Co-Project Director	5	
B. A. Diwan, Research Associate	50	
Technical		
R. F. Norberg, Research Assistant	15	REDACTED
Eugene Farrin, Research Assistant	20	
Animal Caretaking		
Secretarial Assistance		
Sub-Total		REDACTED
Employee benefits: 16%		
B. Consumable Supplies (list by categories)		
Chemicals, glassware, instruments		1,000
Food and Bedding		900
Sub-Total		1,900
C. Other Expenses (itemize)		
Domestic travel to scientific meetings		250
Publication Costs		200
Art, Photo, and Replicating Service		200
Histotechnical Service		1,000
Mouse Purchases		1,400
Sub-Total		3,050
D. Permanent Equipment (itemize)		
None		
E. Overhead (15% of A+B+C)		3,321
Total		$25,461

Estimated Future Requirements:

	Salaries	Consumable Suppl.	Other Expenses	Permanent Equip.	Overhead	Total
Year 2	R	$2,000	$3,275	-	$3,523	$27,010
Year 3	R	$2,100	$3,500	-	$3,728	$28,584

It is understood that the applicant and institutional officers in applying for a grant have read and found acceptable the Council's "Statement of Policy Containing Conditions and Terms Under Which Project Grants Are Made."

Signature Hans Meier
Director of Project

Signature
Business Officer of the Institution

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Telephone
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Other Sources of Financial Support

List financial support for research from all sources, including own institution, for this and/or related research projects.

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Title of Project	Source	Amount	Duration
ncogenesis in the rabbit: genetic susceptibility, vertical ransmission of virus, and environmental influences.	The Council for Tobacco Research, U.S.A.	$ 23,310	6/1/73-5/31/74
latural occurrence of RNA tumor virus (genomes) and host-gene control of their expressions.	National Cancer Institute	400,000	5/1/73-4/30/74
Hereditary diseases and variations of the rabbit.	NIH General Research Support grant to the Jackson Laboratory	41,731*	7/1/73-12/31/73
abbit inbred and mutant stocks resource.	NIH Division of Research Resources	25,000*	1/1/73-12/31/73

ending

ncogenesis in the rabbit: genetic susceptibility, vertical ransmission of virus, and environmental influences.	The Council for Tobacco Research, U.S.A.	24,401	6/1/74-5/31/75
Hereditary diseases.	National Institute of General Medical Sciences	35,315*	5/1/74-4/30/75
abbit inbred and mutant stocks resource.	NIH Division of Research Resources	98,015*	1/1/74-12/31/74

*Direct costs

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6. Objectives and specific aims

The objectives of this investigation are to analyse the transplacental embryotoxic, teratogenic, and carcinogenic effects of two classes of nitrosocompounds, nitrosoureas and nitrosamines, in inbred strains of mice and rabbits. Obviously, these studies are complex, and some narrowing of aims is necessary. Thus, we propose to evaluate the action of the compounds with respect to (1) their retention, activation (conversion), and degradation, (2) the role of fetal age or gestational days, and (3) the mode of inheritance and number of genetic loci involved in species and strain differences. We feel that detailed definition of these goals is pertinent to the situation in man: (a) malformations, congenital tumors, and childhood cancers may have been transplacentally induced, and (b) at least certain types of tumors in adults may be due in part to delayed consequences of carcinogen-exposure during intrauterine life.

Strains of mice chosen for study are: AKR/J, DBA/2J, SWR/J, C57BL/6J, and C57L/J; they differ from one another by genetic origin (except for the last two), type C RNA tumor virus expression, inducibility of aryl hydrocarbon hydroxylase (AHH), and sensitivity to 1-ethyl-1-nitrosourea (ENU)-induced teratogenicity and carcinogenicity among other traits. For studies with rabbits we are primarily focusing on strains III and WH because of their differences in genetic origin and AHH inducibility.

7. Working hypothesis

Transplacental exposure is an extremely sensitive method for study of the biological effects of potentially harmful pollutants. Their effects depend upon hereditarily determined differences in susceptibility or resistance of pregnant mothers and embryos, and the stage of fetal (organ) development.

8. Experimental design and procedures

1. Introduction. The potential hazard to man and animals of environmental pollutants is becoming increasingly apparent both upon acute and chronic exposure. Since developing fetuses are particularly susceptible, malformations, congenital and childhood cancers, as well as tumors in adults, may in part be due to consequences of intrauterine chemical injury. Transplacental embryotoxic, teratogenic, or carcinogenic effects have been demonstrated experimentally for numerous compounds particularly polycyclic hydrocarbons and nitrosocompounds. Differences in their effects and causes have been conjectured as due to consequences of species, gestational stage, dosage, and mode of action. Very few studies concern detailed investigations of multiple variables including genetic analyses. Because of the widespread occurrence of nitrosocompounds in industrial pollution, foods, e.g. cured meat, smoked fish, etc., and tobacco products, we wish to gain a better understanding of their specific biological effects.

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The discovery of the toxic effects and carcinogenicity of N-nitrosocompounds was purely accidental. For example, dimethylnitrosamine (DMNA) had been incriminated as the cause of a high incidence of liver cirrhosis among workers of an English factory (1). Aside from and in addition to toxic effects, administration of DMNA to rodents readily produced hepatic carcinomas (2). Depending upon the dose, route, and type of compound an entire spectrum of tumors has been induced in different species including neurogenic tumors with urea derivatives or acyl-alkyl nitrosamides (3). Smoke condensates contain up to nine different nitrosamines depending upon the

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type of cigarette, and their level(s) is related to those of total volatile bases and the tobacco nitrate content (4).

Our aims will focus initially on acute studies, using single transplacental administration of the various N-nitrosocompounds. They will then be extended to chronic low-level exposures during the entire duration of pregnancy, including pretreatments of prospective mothers.

2. Details of Experimental Design and Procedure. There are two classes of nitrosocompounds with respect to their mode of action, (a) nitrosoureas that are direct-acting, or proximate carcinogens and (b) nitrosamines that require metabolic modification. We wish to study the transplacental effects of the two nitrosamines, dimethyl- and diethylnitrosamine (DMNA and DENA) relative to 1-ethyl-1-nitrosourea (ENU). Whereas metabolic activation of DMNA and DENA apparently involves oxidative dealkylation, the outcome of ENU-induced effects most likely depends on genetically determined differences in the cellular repair mechanism rather than its metabolism or transplacental uptake. Since enzyme synthesis is generally repressed in fetal tissues, but related to the stage of differentiation, the carcinogenic effects of DMNA and DENA are probably more rigorously stage- and strain-dependent than those of ENU. Thus, the relationship of fetal enzymatic competence and the genetically dependent expression of endogenous type C-RNA tumor virus may be more precisely identified than in case of ENU. Also, certain of the strains used for these studies are aryl hydrocarbon hydroxylase (AHH)-inducible (C57L/J, C57BL/6J, SWR/J, SWR/J), whereas others (DBA/2J, AKR/J) are not. Apparently high levels of AHH depress DMNA-demethylase.

Studies in inbred strains of mice

1-ethyl-1-nitrosourea. Single intraperitoneal injections of 0.5 mmoles/kg of 1-ethyl-1-nitrosourea (ENU) were given to mice of strains C57L/J, C57BL/6J, SWR/J, DBA/2J, and AKR/J on days 8 and 12 of gestation, and fetuses examined on day 14 or after birth. Both the frequency and severity of ENU-induced malformations varied with the stage of embryogenesis and the strain of mice; the strains of mice are listed in decreasing order of susceptibility (5). Tumors were produced upon treatment of the same strains on days 14, 16, and 18 of gestation. Again, the incidence, types, and latency periods of the induced tumors were strain- and age-dependent, but the susceptibility to transplacental ENU-carcinogenesis was inverse to that for ENU--teratogenesis (6). Assays for the expression of type C RNA tumor virus or its group-specific antigen (gs-AG) in tissues of different strains of mice indicated that (a) viral activation occurred in mice after transplacental administration of ENU, (b) a significant association existed between gs-AG and in some cases complete virus expression and ENU-induced tumors, and (c) the rate of tumor induction and gs-AG or virus expression was influenced by the host genotype or strain of mice (7). Reciprocal F_1 hybrids of strains AKR/J and SWR/J were exposed to transplacental treatment of ENU on day 16 of gestation. A pronounced maternal influence on the development of tumors was observed. Thus (SWR/J ♀ x SWR/J ♂)F_1 offspring were found to be more susceptible to the induction of lung tumors and leukemia (latency 10 weeks or less) by ENU than the offspring of (AKR/J ♀ x SWR/J ♂)F_1 mice (16 to 20 weeks). Because of the consistently high incidence of development of multiple (two or more types of) tumors within a short period of time, (SWR/J ♀ x AKR/J ♂)F_1 mice provide a highly sensitive model for the simultaneous testing of anti-type C RNA tumor viral vaccines against both mesenchymal and epithelial tumors (8).

Chronic low dose ENU exposure of mice during the entire course of pregnancy

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and of prospective mothers has not yet been investigated.

Dimethyl- and diethylnitrosamine. The importance of fetal metabolizing enzymes relative to the effects of DMNA and DENA may best be studied upon administration of these compounds at various gestational days, i.e. 12, 14, 16, and 18 days. Apparently, their role is reflected in the formation of alkylating intermediates following dealkylation by microsomal mixed oxidase enzymes. According to Preussmann et al. (9), the amount of formaldehyde liberated from fetal liver- and kidney-microsomes can be used to determine the activity of DMNA-demethylase. We plan to utilize a modification of the demethylase assay of Ventkatsan et al. (10) and determine the extent of formaldehyde-liberation from isolated microsomes following the procedure of Chochin and Axelrod (11); protein will be estimated by a microbiuret method (12).

DENA-dealkylation will be determined in fetal livers and kidneys using procedures described by Preussmann et al. (9) and Stotz (13); this method is based upon a color-reaction of acetaldehyde with a copper sulfate-p-hydroxy-biphenyl reagent.

Embryotoxicity, teratogenicity, and carcinogenicity assays will be performed in treated versus control (vehicle-injected) mice. Standard genetic analyses will be conducted for possible correlations between dealkylating activity by organ, gestational days, and organ-specific tumorigenesis.

Studies in rabbits

1-ethyl-1-nitrosourea. Our preliminary results on the effects of ENU in strain-crosses segregating for alleles at the Ah locus tend to indicate a possible association with AHH inducibility, despite the fact that the fetal genotype appears irrelevant. If strain differences in dealkylation, tumor induction, and virus-expression are observed, genetic analyses may provide us with answers to their mode of inheritance and the number of genes involved.

Strain III_{vo} and III_{mo} fetuses are highly susceptible to ENU-induced renal tumors when pregnant mothers are treated on day 18 of pregnancy; multiple tubular adenomas and adenocarcinomas develop as early as 40 days after birth. These tumors occur reproducibly and within a limited time, and provide us with an opportunity to search for endogenous rabbit C-type tumor virus(es) as outlined in CTR-RENEWAL APPLICATION 758. Pregnant rabbits of two partially inbred strains III and WH were injected intraperitoneally with a single dose of 60 mg/kg of ENU in trioctanoin on day 18 of gestation. Controls were treated on the same day with solvent alone. Tumors developed in almost all offspring of strain III that survived more than 8 weeks. In contrast, no such tumors have yet developed in offspring of strain WH (14). Renal tumors developed in offspring of strain III rabbits at an exceptionally high incidence (70%). Induction time ranged from 40 days to 135 days. Kidney tumors, either renal adenomas or adenocarcinomas appeared to develop within cysts occurring in subline III_{vo} because of homozygosity for a recessive gene causing renal cyst formation (rc).

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Dimethyl- and diethylnitrosamine. The procedural details are analogous to those described for mice. With respect to retention, conversion, and degradation of N-nitrosocompounds, a number of radiolabels for their radicals are available for analysis. Also, the nitroso-tumor models are highly suitable for testing the "oncogene" hypothesis (see RENEWAL APPLICATION 758) since virus-particles (type C?) have been observed on a few occasions even in neurogenic tumors, although their significance in the pathogenesis of experimental tumors is as yet unknown.

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Methylcholanthrene (MCA) induced amino azo N-demethylase and represses DMNA-N-demethylase synthesis in rat livers (15). These findings were used to explain the fact that hepatocarcinogenesis was not enhanced by simultaneous treatment with MCA and DMNA (16). However, synergetic effect was found with respect to lung tumorigenesis in rats; also the combined application of MCA and DMNA in mice lead to a higher overall tumor incidence than found by either DMNA or MCA application alone (17). Thus, remarkable species and organ differences were found in rats and mice. In order to resolve this situation, it is essential to study this system in other species of laboratory animals. We, therefore, plan to investigate the combined effects of MCA and DMNA in rabbits with respect to their possible syncarcinogenicity, using AHH-inducible strain III and AHH-noninducible strain WH.

3. Significance of this research. Products necessary for the synthesis of nitrosocompounds occur in the environment (18, 19). For example, nitrosamines are readily produced upon reaction of nitrous acid or sodium nitrite on secondary amines or alkylamides. Nitrite- and nitrate-yielding substances occur in a variety of drugs and food additives. Secondary amines and alkylamides are also widespread, e.g., in bacteria, fish, etc., (20, 21), and are produced during cooking processes. A number of them are used as industrial solvents and neutralizing agents. Nitrosamines have also been detected in tobacco smoke, especially in smoke from cigarettes containing a high content of nitrate (4, 22). Apparently nitrogen oxide (nitric oxide and nitric dioxide) and volatile bases of tobacco smoke are the precursors of N-nitrosamines. Oxides of nitrogen may react with secondary amines, particularly nornicotine and anabasine of smoke to form nitrosoanabasine and nitrosonornicotine (23).

Our current studies in rabbits with 1-ethyl-1-nitrosourea show that primary renal tumors, i.e., papillary cyst-adenomas and mixed Wilms'-like nephroblastomas, can readily be induced in strain III rabbits with a single dose of ENU given on day 18 of pregnancy. Apparently, the incidence and inducibility depend upon the presence or absence of homozygosity for a gene, rc, responsible for renal cortical cyst formation (24). The occurrence and distribution of this gene is high in subline III_{vo} and low in subline III_{mo}; it is absent in strain WH. The pathogenic significance of renal cyst formation to primary renal tumor induction is indicated by both the origin of the tumors from cyst epithelium and their multicentricity. Thus, whereas genotypic differences are of obvious importance to renal tumorigenesis, susceptible strain III_{vo} rabbits develop renal tumors even when given a single intraperitoneal injection of ENU at 8 weeks of age (unpublished results). We are now analysing the effects of other classes of carcinogens including different nitrosocompounds on the susceptibility or resistance to renal tumor development in strain III rabbits. Also, genetic analyses of renal tumor susceptibility are in progress utilizing all possible crosses between strains III and WH.

It is noteworthy that we have found a single case each of nephroblastoma or Wilms' tumor in old WH and strain III rabbits (25); yet, strain WH is entirely resistant to the transplacental induction of renal tumors, whereas strain III appears to be highly susceptible. The only other case of spontaneous Wilms' tumor occurred in a strain AC rabbit. In contrast, none were ever found in strains OS, ACEP, AX, A, C, III_c, and hybrids between III and III_c (25). Thus, the occurrence of spontaneous and induced primary renal tumors, including Wilms'-like tumors in rabbits is genotype-dependent. Although the frequency of Wilms' tumors is low in man, the occurrence in clusters among sibships, families, successive generations, and identical twins also suggest an hereditary tendency (26-32). A critical relationship between tumor-induction or occurrence and renal cyst formation could exist in man as well as the rabbit because polycystic renal disease of man is known

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to have a hereditary basis (33).

We feel that strain III rabbits are a suitable and useful model for the study of two related primary renal tumors, because of (a) a targeted organ susceptibility, (b) their consistent and rapid inducibility, and (c) the size(s) of the induced tumors. Finally, since both polycyclic hydrocarbons and nitrosocompounds occur in the environment, their combined (syncarcinogenic) effects may potentiate the consequences of intrauterine exposure. Such a synergism may be important both with respect to fetal teratogenesis and carcinogenesis in smoking mothers as hydrocarbons and nitrosamines are present in cigarette smoke.

To date, the best known example of transplacental carcinogenesis in man is the frequent occurrence of vaginal adenocarcinoma in young women whose mothers were treated with diethylstilbestrol for the prevention of abortion. Other tumors suspect of transplacental induction are such childhood cancers as leukemias, retinoblastoma, and neuroblastoma, in addition to Wilms' tumors or nephroblastomas. Some of these tumors are also associated with a variety of congenital anomalies, including aniridia, hemihypertrophy, and malformations of the genito-urinary tract. In animals, the most common effects of chemical carcinogens and teratogens is an increase in the incidence of specific lesions (tumors and malformations) to which they are inherently susceptible; yet, these are notable exceptions. At least for leukemogenesis in inbred strains of mice the co-participation of chemicals and endogenous type C RNA tumor viruses is now well recognized.

4. References

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7. DIWAN, B. A., H. MEIER, and R. J. HUEBNER. Transplacental effects of 1-ethyl-1--nitrosourea in inbred strains of mice: III. Activation of infectious or subinfectious endogenous type C RNA tumor virus in spleens and tumors of different strains of mice. J. Nat. Cancer Inst. (in press).

8. DIWAN, B. A., H. MEIER, and R. J. HUEBNER. Transplacental effects of 1-ethyl-1--nitrosourea in inbred strains of mice: IV. Rapid tumor induction in strain crosses. J. Nat. Cancer Inst. (in press).

9. PREUSSMANN, R., A. VON HODENBERG, and H. HENGY. 1968. Mechanism of carcino-

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genesis with 1-aryl-3,3 dialkyltriazenes. Enzymatic dealkylation by rat liver microsomal fraction in vitro. Biochem. Pharmacol. 18:1-13.

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Biographical sketches of all principal and professional personnel

Hans Meier

Born: REDACTED

Nationality: REDACTED

Education:

University of Zurich (Veterinary Medicine), D.V.M. REDACTED

University of Zurich (Pathology) Dr. med. vet. REDACTED

Harvard School of Public Health REDACTED

Massachusetts Institue of Technology, Alumnus (Biophysical and biochemical cytology, biology) REDACTED

Honors:

Royal Society of Health (Pharmacology), M.R.S.H. 1963

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	Member, Scientific Advisory Board, The Council for Tobacco Research, USA	1971-
	Member, Solid Tumor-Virus Working Group, Special Virus-Cancer Program, National Cancer Institute, NIH	1971-1973
	Member, Breast Cancer Virus Segment, National Cancer Institute, NIH	1973-
Major Interests:	Experimental pathology, cancer	
Positions:		
1970-	The Jackson Laboratory, Senior Staff Scientist	
1970-	The National Cancer Institute, Consultant	
1962-70	The Jackson Laboratory, Staff Scientist	
1960-62	The Jackson Laboratory, Associate Staff Scientist	
1957-60	Harvard Medical School, Res. Asst. (Pathology)	
1958-60	Children's Hospital and Medical Center, Boston, Asst. (Experimental) Pathologist	
1957-60	Children's Cancer Research Foundation Res. Asst., Res. Assoc. (Exp. Pathol.)	
1954-57	Angell Memorial Hospital, Boston, Fellow, Resident, Chief of Pathology	
Postgraduate training:		
1955-57	Harvard Medical School, Course work in pathology and neuro-pathology	
1957	Harvard University, Summer School of Arts and Sciences, and of Education (Biophysics and radioactive measurements)	
1958	Armed Forces Institute of Pathology (Course in histochemistry)	
1959	Harvard University, Depts. Biology, (Electron microscopy) and Chemistry (Experimental methods in biochem.)	

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R: REDACTED MATERIAL

Societies:

REDACTED

Richard R. Fox

Born:

Nationality:

REDACTED

Educated:

University of Connecticut (Animal Production) B.S. REDACTED

University of Minnesota (Animal Breeding) M.S. REDACTED

University of Minnesota (Animal Breeding and Genetics) Ph.D. REDACTED

The Jackson Laboratory (Rabbit Genetics), Postdoctoral Fellow REDACTED

Honors:

B.S., with honors and with distinction in Animal Production

Sigma Xi

Gamma Sigma Delta

Alpha Zeta

Member: Committee on Nomenclature for Inbred Rats, Hamsters, Gerbils, and Rabbits, Nat. Acad. Sci., ILAR

Major interests:

Genetics of the rabbit; quantitative genetics; reproductive physiology; animal husbandry

Positions:

1965-	The Jackson Laboratory, Staff Scientist
1961-	University of Maine, Department of Animal and Veterinary Science, Lecturer
1960-65	The Jackson Laboratory, Assoc. Staff Scientist

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R: REDACTED MATERIAL

Societies:

REDACTED

Bhalchandra Apparo Diwan

Born: REDACTED

Nationality: REDACTED

Education:

Willingdon College, Sangli, B.Sc. (Gen.)	REDACTED 1956
University of Poona B.Sc. (Hons.) M.Sc. Ph.D.	REDACTED

Academic honors:

Recipient of an award for highest marks in chemistry, Willingdon College, Sangli, India	1959
Research scholar of Govt. of India, Ministry of Education, New Delhi, India	1961-1966

Major interests: Viral-chemical cocarcinogenesis, embryology

Positions:

1971-	The Jackson Laboratory Postdoctoral Trainee
1967-1971	Cancer Research Institute, Parel, Bombay, Scientific Officer
1966-1967	Vivekanand College, Kolhapur Professor of Zoology
1964-1966	Indian Council of Medical Research, New Delhi, India Postdoctoral Fellow

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Relevant publications

MEIER, H., D. D. MYERS, and R. J. HUEBNER. 1969. Genetic control by the hr-locus of susceptibility and resistance to leukemia. Proc. Nat. Acad. Sci., USA 63:759-766.

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